(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization

International Bureau



TERRECORD CONTRACTOR OF THE CO

(43) International Publication Date 5 August 2004 (05.08.2004)

PCT

(10) International Publication Number WO 2004/065351 A1

- (51) International Patent Classification⁷: C07C 237/42, 275/34, 271/28, 237/30, C07D 215/08, 217/06, C07C 255/57, C07D 213/82, A61K 31/167, 31/277, 31/4406, 31/17, 31/27, 31/166, 31/4709
- (21) International Application Number:

PCT/EP2004/000571

- (22) International Filing Date: 23 January 2004 (23.01.2004)
- (25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/442,532

24 January 2003 (24.01.2003) US

- (71) Applicant (for all designated States except AT, US): NO-VARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).
- (71) Applicant (for AT only): NOVARTIS PHARMA GMBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): COPPOLA, Gary, Mark [US/US]; 18 Aldersgate Circle, Budd Lake, NJ 07828 (US). DAMON, Robert, Edson [US/US]; 13 Jordan Road, Hopkinton, MA 01748 (US). KUKKOLA, Paivi, Jaana [FI/US]; 17 Steeplechase Lane, Asbury, NJ 08802 (US). STANTON, James, Lawrence [US/US]; 8 Cedar Street, Charlestown, MA 02129 (US).

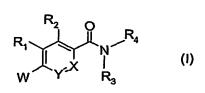
- (74) Agent: GRUBB, Philip; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AMIDE DERIVATIVES AND THEIR USE AS INHIBITORS OF 11-BETA-HYDROXYSTEROID DEHYDROGE-NASE TYPE 1



(57) Abstract: Compounds of the formula (I) provide pharmacological agents which lower intracellular glucocorticoid concentrations in mammals, in particular, intracellular cortisol levels in humans. Therefore, the compounds of the instant invention improve insulin sensitivity in the muscle and the adipose tissue, and reduce lipolysis and free fatty acid production in the adipose tissue. The compounds of the invention lower hepatic glucocorticoid concentration in mammals, in particular, hepatic cortisol concentration in humans, resulting in inhibition of hepatic gluconeogenesis and lowering of plasma glucose levels. Thus, the compounds of

the instant invention may be particularly useful in mammals as hypoglycemic agents for the treatment and prevention of conditions in which hyperglycemia and/or insulin resistance are implicated, such as type-2 diabetes. The compounds of the invention may also be used to treat other glucocorticoid associated disorders, such as Syndrome-X, dyslipidemia, hypertension and central obesity. The invention furthermore relates to the use of the compounds according to the invention for the preparation of medicaments, in particular of medicaments useful for the treatment and prevention of glucocorticoid associated disorders, by improving insulin sensitivity, reducing plasma glucose levels, reducing lipolysis and free fatty acid production, and by decreasing visceral adipose tissue formation.

O 2004/065351 A